Remarks

After entry of the amendment, claims 1-11, 13-15 and 17-24 are pending.

Claim 16 has been canceled without prejudice as being redundant of claim 1.

Claim 12 has been canceled without prejudice and replaced with new claims 21-23. In view thereof, Applicant respectfully requests that the rejection under 35 USC § 112, second paragraph, be withdrawn.

No issues of new matter should arise and entry of the amendment is respectfully requested.

Rejection under 35 USC § 102

Claim 17 is rejected under 35 USC § 102(b) as being anticipated by Rupreht et al, *Anesthesiology*, 58:524-526 (1983).[1]

Applicant respectfully traverses the rejection and respectfully submits that Rupreht is unrelated to the claimed invention.

Applicant respectfully submits that Rupreht is concerned with the symptoms some patients experience upon awakening from anesthesia, where the anesthesia is nitric oxide. There is no evidence that "nitric oxide withdrawal syndrome," caused by anesthesia, is related to the presently claimed "substance abuse." The PTO asserts, without any factual evidence to support the assertion, that one skilled in the art would consider nitric oxide for anesthesia to be a substance that would be abused. Applicant respectfully requests that the PTO provide evidence in the form of a journal article, publication or patent to support this unsubstantiated conclusory opinion.

Applicant respectfully submits that one skilled in the art would not consider a patient receiving anesthesia with nitric oxide to be abusing a substance (i.e., nitric oxide). Rupreht is solely concerned with treating the symptoms caused by anesthesia, not with treating substance abuse. Accordingly, Rupreht does not anticipate the claimed invention.

In view of the above, Applicant respectfully requests that the rejection under 35 USC § 102 be withdrawn.

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[1] A copy of the entire journal article is submitted in the Information Disclosure Statement filed herewith.

Rejection under 35 USC § 103

Claims 1-20 are rejected under 35 USC § 103 as being obvious over US Patent No. 4,895,841 to Sugimoto et al in view of Arendt et al (Acta Neurobiol Exp, abstract) or Rupreht et al, *Anesthesiology*, 58:524-526 (1983)[2] in view of Hurlbut, *Psychiatric Aspects of Emergency Medicine*, 9(1):31-52 (1991).[3]

Applicant notes that the PTO did not provide a copy of Arendt et al (Acta Neurobiol Exp, abstract) with the Office Action; did not cite Arendt et al (Acta Neurobiol Exp, abstract) in the Form PTO-892; did not provide the full citation for Arendt et al (Acta Neurobiol Exp, abstract); and did not address the teachings in Arendt et al (Acta Neurobiol Exp, abstract) in rejecting claims 1-20 in the office action. Accordingly, Applicant cannot address Arendt et al (Acta Neurobiol Exp, abstract) because it appears that the PTO did not rely on this reference to reject the pending claims and because Applicants cannot locate the reference.

Applicant respectfully traverses the rejection and respectfully submits that the references do not disclose or suggest the claimed invention.

Sugimoto discloses cholinesterase inhibitors, such as donepezil. Sugimoto does not disclose or suggest the claimed invention. Applicant respectfully submits that the PTO mischaracterizes the teachings in Sugimoto. In the Office Action at page 4, lines 4-8, the PTO incorrectly asserts that "Sugimoto teaches that the compounds are useful in the treatment of diseases or conditions that are thought to be associated with deficiency of acetylcholine (col. 1)." Also in the Office Action at page 5, lines 1-3, the PTO mischaracterizes the teachings in Sugimoto by stating "Sugimoto teaches that the claimed compounds are more effective than the conventionally used physostigmine and other conventional anticholinesterase inhibitors." Again, the PTO mischaracterizes the teachings in Sugimoto by greatly exaggerating and over generalizing what Sugimoto actually states. Sugimoto teaches the following at column 1, lines 39-60 (Emphasis Added):

> Specifically, the compound of the present invention represented by the following general formula (I) has great advantages of having strong and highly selective antiacetylcholinesterase activity, increasing the amount of acetylcholine present in the brain, exhibiting an excellent effect on a model with respect to disturbance of memory, and having a persistent activity and a high safety when

[2] A copy of the entire journal article is submitted in the Information Disclosure Statement filed herewith.
[3] A copy of the entire journal article is submitted in the Information Disclosure Statement filed herewith.

> compared with physostigmine which is a conventional popular drug in the art, which renders the compound of the present invention very valuable.
>
> The compound of the present invention was found based on the acetylcholinesterase inhibitory action and, therefore, ***is effective for treatment and prevention of various diseases which are thought to be derived from the deficiency of acetylcholine*** as a neurotransmitter in vivo.
>
> Examples of such diseases include various kinds of dementia including Alzheimer senile dementia and further include Huntington's chorea, Pick's disease, and ataxia.

The PTO fails to mention that Sugimoto teaches that the compounds described therein are useful for treating Alzheimer senile dementia, Huntinton's chorea, Pick's disease and ataxia. Moreover, Sugimoto teaches that compounds of formula (I) (e.g., donepezil) are more effective than conventional drugs (e.g., physostigmine) in "a model with respect to disturbance of memory." There is no evidence of record that the presently claimed "substance abuse" is a type of dementia as described by Sugimoto.

Rupreht and Hurlbut do not cure the deficiencies of Sugimoto, and Hurlbut does not cure the deficiencies of Sugimoto in view of Rupreht.

Rupreht is concerned with the symptoms some patients experience upon awakening from anesthesia, where the anesthesia is nitric oxide. There is no evidence that "nitric oxide withdrawal syndrome," caused by anesthesia, is related to the presently claimed "substance abuse." The PTO asserts, without any factual evidence to support their assertion, that one skilled in the art would consider nitric oxide for anesthesia to be a substance that would be abused. Moreover, there is no evidence of record (except for the PTO's conclusory, unsubstantiated statements) that nitrous oxide withdrawal symptoms bear any relationship to substance abuse or symptoms associated with substance abuse. Applicant respectfully requests that the PTO provide evidence in the form of a journal article, publication or patent to support this unsubstantiated conclusory opinion.

Applicant respectfully submits that one skilled in the art would not consider a patient receiving anesthesia with nitric oxide to be abusing a substance. Rupreht is solely concerned with treating the symptoms caused by anesthesia, not with treating substance abuse. Accordingly, Rupreht is wholly unrelated to the claimed invention.

Hurlbut does not disclose or suggest the use of cholinesterase inhibitors for treating drug-induced psychoses caused by cocaine, amphetamines, lysergic acid diethylamide, phencyclidine, cannabinoids, mescaline, hallucinogenic mushrooms, designer drugs, or steroids.

Hurlbut only discusses the use of physostigmine, a cholinesterase inhibitor, with respect to anticholinergic drugs. At page 49, Hurlbut states:

> Physostigmine is a reversible acetylcholinesterase.... It is useful in confirming the diagnosis of anticholinergic poisoning by reversing both central and peripheral manifestations. ... The use of physostigmine has been associated with several adverse reactions, most commonly, seizures, which are usually seen after rapid IV injection. Thus, the drug is not indicated merely because a history of anticholinergic ingestion is obtained. Relative chontraindications to its use include a history of asthma, gangrene, significant cardiovascular disease, and obstruction of the gastrointestinal or urogenital tract. Patients receiving physostigmine should be carefully monitored for evidence of cholinergic toxicity including bradycardia, miosis, salivation, sweating, abdominal cramping, vomiting, diarrhea, urination, general weakness, fasciculations, paralysis, excessive tracheobronchial and salivary secretions, bronchospasms, and laryngospasm. Physostigmine is rapidly metabolized aand [sic] effects generally wear off after 30 to 60 minutes. Clinical judgment must be used in deciding whether the risk of repeated injections in an individual patient is warranted or whether the patient would be better served by sedation with benzodiazepines and general supportive measures.
>
> The use of physostigmine in tricyclic antidepressant overdoses has been associated with convulsions and asystole and is probably best avoided.

As can be seen from the above description in Halburt, physostigmine is not an optimal choice for treating anticholinergic poisoning.

Applicant respectfully submits that the PTO mischaracterizes the teachings in Hurlbut in the Office Action at page 4, lines 16-19 as follows:

> Hurlbut teaches ... specific antidotes such as physiostigmine for anti-cholinergic poisoning or urinary acidification to enhance excretion of amphetamines or phencyclidine in some patients.

Applicant respectfully submits that Hurlbut does not describe any relationship between physostigmine and urinary acidification, and that the PTO has not established any relationship between physostigmine and urinary acidification. The reference to "urinary acidification" in the Office Action is wholly irrelevant to the claimed invention.

Again, contrary to the assertions in the Office Action, the discussion of amphetamines in Hurlbut at pages 36-38 does not disclose or suggest any cholinesterase inhibitor as a form of treatment. Hurlbut does state "While urinary acidification has at times been suggested as a method to enhance elimination of amphetamines, the efficacy of this maneuver in terms of clinical outcome is quite controversial. As cardiovascular complications of plasma acidification may develop in overdose conditions, it is generally not recommended." The PTO has not established any relationship between urinary acidification and cholinesterase inhibitors. The record is devoid of any evidence that urinary acidification has anything to do with cholinesterase inhibitors. Moreover, the evidence demonstrates that urinary acidification is not a recommended treatment for the elimination of amphetamines from a patient. Applicant respectfully submits that the PTO's reference to amphetamines and urinary acidification is wholly unrelated to the presently claimed invention.

Again, contrary to the assertions in the Office Action, the discussion of phencyclidine in Hurlbut at pages 39-43 does not disclose or suggest any cholinesterase inhibitor as a form of treatment. Hurlbut does state: "Urinary acidification enhances renal excretion of PCP; however, the clinical effectiveness of this in overdose patients is unproven, and it is generally believed that the risks of acidification outweigh the potential benefits." Again, the PTO has not established any relationship between urinary acidification and cholinesterase inhibitors. The record is devoid of any evidence that urinary acidification has anything to do with cholinesterase inhibitors. Moreover, the evidence demonstrates that urinary acidification is not a recommended treatment for the elimination of phencyclidine from a patient. Applicant respectfully submits that the PTO's reference to phencyclidine and urinary acidification is wholly unrelated to the presently claimed invention.

With respect to claim 15, none of the cited references disclose or suggest methods for decreasing the rate of relapse in a patient who had been previously addicted to an addictive substance by administering a cholinesterase inhibitor, such as donepezil. Accordingly, the PTO has not established a *prima facie* case of obviousness for claim 15, such that the rejection must be withdrawn.

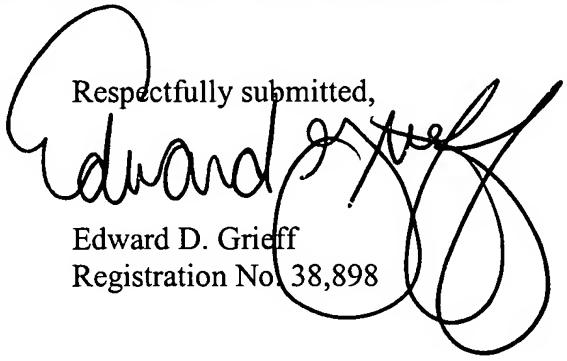
Applicant respectfully submits that the present rejection is based on an improper hindsight analysis and improper leaps in logic in what the cited references actually teach. The

PTO randomly picks and chooses various teachings from the various references to reject the claims. The PTO has not established a *prima facie* case of obviousness, and has not established any motivation to use a cholinesterase inhibitor or donepezil in the presently claimed methods. In view thereof, Applicant respectfully requests that the rejection under 35 USC § 103 be withdrawn.

Conclusion

An early and favorable reconsideration and allowance of claims is respectfully requested. The Examiner is encouraged to contact the undersigned to expedite prosecution of this application.

Respectfully submitted,



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